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Combinatorial Chemistry - An Online Journal 12 (2010) 13–16

Contents lists available at ScienceDirect

Combinatorial Chemistry - An Online Journal

journal homepage: www.elsevier.com/locate/comche

Combinatorial Chemistry Online

Volume 12, Issue 4, April 2010

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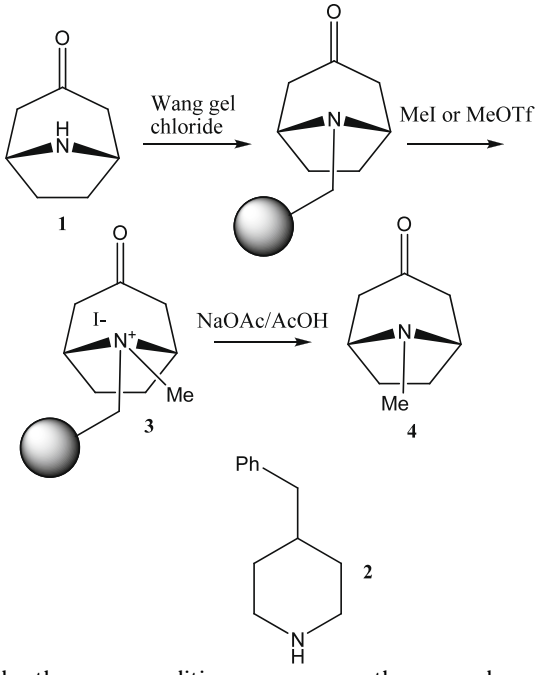
1. Current literature highlights

1.1. Solid-phase synthesis of N-methyl amines

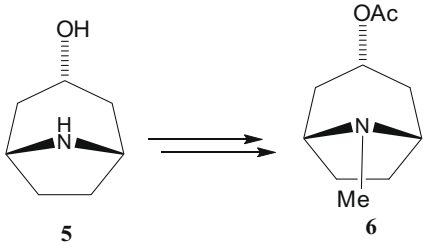
Solid-phase supports are widely used for rapid, parallel library synthesis of a range of compound types. To maximise the impact of solid-phase methodology, it has to be able to readily prepare a sufficiently wide range of appropriate functionality in the final products, including a clean and efficient cleavage from the solid support with additional functionalisation as required. Tertiary amines are widely found in a number of biologically important compounds. In particular the *N*-methyl group is commonly found, including in the structures of the tropane alkaloids.

A recent paper describes an efficient route to *N*-methylated tertiary amines, in which the methylation takes place as the compounds are cleaved from the solid support. The reaction, based on quaternisation and nucleophilic debenzylation, has been demonstrated through the synthesis of tropane alkaloid mimetics.[1]

Cyclic secondary amines such as that found in nortropinone (**1**) can be immobilised through the nitrogen on a number of solid-supported linker groups including the REM, Wang and BAL linkers, but the conditions required for cleavage are often incompatible with other functionality or reactions on the molecule. However, it was found that both nortropinone (**1**) and 4-benzylpiperidine (**2**) could be anchored on Wang resin previously activated by thionyl chloride (Wang gel chloride). Quaternisation of the amines with methyl iodide or methyl triflate gave an *N*-methylammonium iodide (or triflate) intermediate (**3**). Cleavage could be achieved with a variety of nucleophiles, although sodium acetate in acetic acid at 100 °C proved to be the most effective method for both substrates, giving the *N*-methylated tertiary amines (e.g. **4**).



Under the same conditions, numerous other secondary amines were readily converted to *N*-methyl tertiary amines on cleavage, and primary amines gave mainly the *N*,*N*-dimethyl derivatives, with slight contamination with the monomethyl product. When applied to nortropine (**5**), the cleavage step also acetylated the hydroxyl group to give the acetate product **6**.



In summary this new method appears to be an effective way to generate *N*-methyl and *N*,*N*-dimethyl tertiary amines in a cleavage

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doi:10.1016/j.comche.2010.03.001

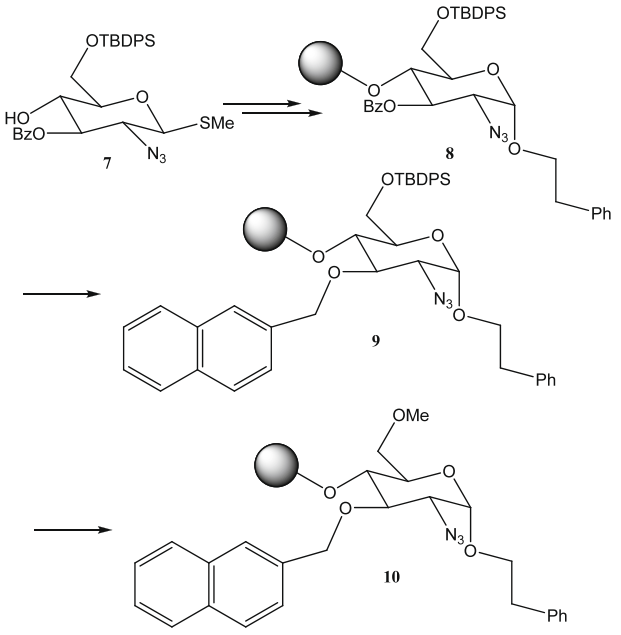
step from Wang resin, and should have wide applications in combinatorial synthesis.

1.2. Versatile route to diversity libraries on a monosaccharide scaffold

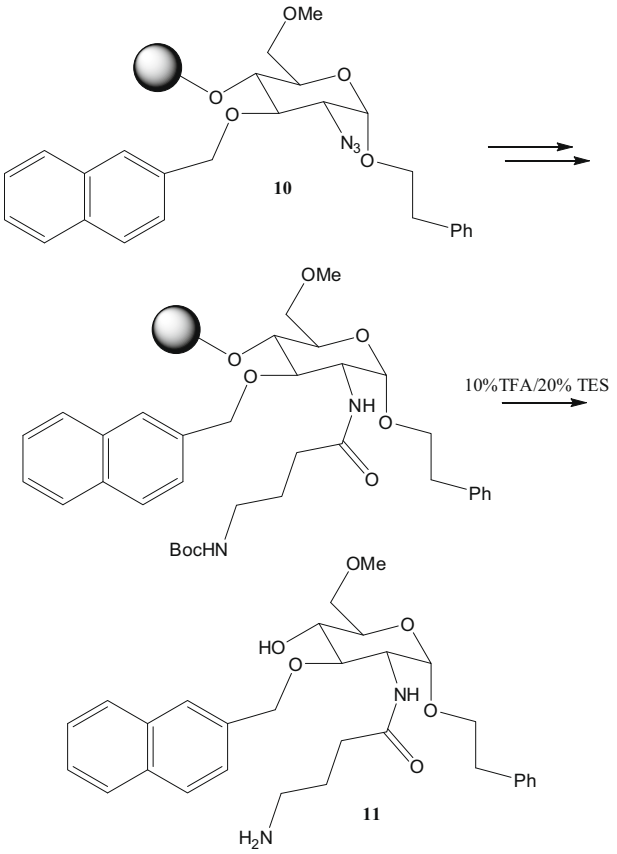
Using a monosaccharide scaffold for the generation of drug-like molecules offers several advantages. The sugar framework presents a number of pharmacophore groups in three-dimensional space in a configurationally predefined orientation. Furthermore, such compounds can possess orthogonally differentiable chemistry and also be prepared on solid support. A recent paper describes a highly flexible approach to the synthesis of pyranose-based library compounds made on solid support.[2]

The authors opted to use a 2-amino functionalised glycopyranoside as the central building block rather than a 2-oxygenated compound, as this simplified the protection strategy and also permitted the use of amide couplings. Additionally, the use of ether substituents was preferred over the precedented carbamate derivates as the former were seen to enhance the drug-like nature of the library products. Compounds were prepared on solid support, and for this purpose the *p*-methoxybenzyl ether linker was chosen, as this offers a highly inert bond that requires oxidising or acidic conditions for cleavage.

The synthetic approach proceeded in a number of steps. Starting with the protected building block **7**, the first step required introduction of an ether substituent (e.g. the phenylethoxy group) at the anomeric position, using the thiophilic reagent, dimethyl (methylthio)sulphonium triflate as the glycosyl promoter. Separation of anomers was followed by loading onto resin through the 4-hydroxy position to give **8**. Step two introduced the R3 group by alkylation of the hydroxy group revealed by Zemplen *O*-deacylation of a benzoate protecting group. The product **9** then underwent desilylation using a proton sponge/HF salt, and a second alkylation introduced the R5 ether substituent to give **10**.



Finally, the azide group in intermediate **10** was reduced by DTT under basic conditions, and acylation of the amine was followed by cleavage from the resin support by 10% TFA in dichloromethane to give the final compound **11**.



This synthetic route has more recently been applied to the preparation of a library of several hundred compounds based on the monosaccharide scaffold and these have been screened against G-protein coupled receptor targets. The authors plan to describe the library preparation and the screening results in a future publication.

2. A summary of the papers in this month's issue

2.1. Solid-phase synthesis

The total synthesis of cyclodecapeptide antibiotics from *Bacillus laterosporus*, laterocidin and its analogues, has been accomplished for the first time by solid-phase peptide synthesis followed by traceless on-resin cyclisation of the linear precursors.[3]

An efficient solid-phase synthesis of *N*-1-alkyl-substituted analogues of cyclic inosine-diphosphate-ribose (cIDPR), a mimic of cyclic ADP-ribose (cADPR), has been reported. The synthetic strategy makes use of a polystyrene support to which inosine was bonded through a 2′,3′-acetal linkage. The cyclisation step was carried out both on solid-phase and in solution by pyrophosphate bond formation, and the effect of the *N*-1-polymethylene chain length on the cyclisation yields were thoroughly investigated.[4]

2.2. Solution-phase synthesis

An efficient method for the synthesis of new polycyclic skeletons: pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-ones and pyrido[2′,1′:2,3]imidazo[5,4-*c*]azepin-7(6*H*)-ones in libraries via Pd-catalyzed intramolecular arylation has been described.[5]

2.3. Scaffolds and synthons for combinatorial libraries

No papers this month.

2.4. Solid-phase supported reagents

A polymer-supported organocatalyst has been prepared by ion exchange reaction of MacMillan iminium catalyst with polymer-supported sulphonic acids. The resulting polymeric organocatalyst was found to be effective for Diels–Alder reaction of 1,3-cyclopentadiene and *trans*-cinnamaldehyde in CH_3OH/H_2O, affording good enantioselectivity and reusability.[6]

A versatile method for fast scavenging a variety of electrophiles in solution phase combinatorial synthesis using carbon nanotubes functionalised by amino groups (CNT–NH_2) has been reported. Following the scavenging event, CNT–NH_2 was easily separated from the reaction mixture by filtration, leaving the desired products in excellent yields and purities.[7]

2.5. Novel resins, linkers and techniques

The natural flavonoid bergenin has been directly immobilised onto carboxylic acid-functionalised controlled pore glass (carboxy-CPG) in 95% yield. Enzymatic cleavage of the 7-bromo-4-butyryl-bergenin derivative from carboxy-CPG has been accomplished using lipase B (LipB) in an aqueous/organic mixture, demonstrating the feasibility of solid-phase biocatalysis of a natural product in aqueous and non-aqueous media.[8]

A novel and facile method for the cleavage of a silicon-based linker on solid-phase supports such as glass plates or silica resin has been described. The linker was efficiently cleaved by oxidation of the silicon–carbon bond (Tamao–Kumada oxidation) to release the functionalised molecule.[9]

A computer program called Privileged Chemical Space Predictor (pcsp) that statistically determines SAR from high-throughput screening (HTS) and combinatorial library data and then identifies features in small molecules that predispose them for binding a target has been described. Features are scored for statistical significance and can be utilised to design improved second generation compounds or more target-focused libraries. The program's utility was demonstrated through analysis of a modularly assembled peptoid library that was previously screened for binding to and inhibiting a group I intron RNA from the fungal pathogen *Candida albicans*.[10]

Several approaches have been developed for screening combinatorial libraries or collections of synthetic molecules as agonists or antagonists of protein function. A recent report describes an experimental platform that seamlessly couples massively parallel bead-based screening of one-bead one-compound combinatorial libraries with microarray-based quantitative comparisons of the binding affinities of the many hits isolated from the bead library.[11]

2.6. Library applications

Using mefloquine as a scaffold, a next generation quinoline methanol (NGQM) library was constructed to identify early lead compounds that possess biological properties consistent with the target product profile for malaria chemoprophylaxis while reducing permeability across the blood–brain barrier. The library of 200 analogues resulted in compounds that inhibit the growth of drug sensitive and resistant strains of *Plasmodium falciparum*.[12]

A small molecule (1835F03) that inhibits *Staphylococcus aureus* wall teichoic acid biosynthesis, a proposed antibiotic target, has been discovered. Rapid, parallel, solution-phase synthesis was employed to generate a focused library of analogues, providing detailed information about structure–activity relationships and leading to the identification of targocil, a potent antibiotic.[13]

The *S′* subsites of human neutrophil proteinase 3 (Pr 3) were probed by constructing diverse libraries of compounds based on the 1,2,3,5-thiatriazolidin-3-one 1,1-dioxide using combinatorial and click chemistry methods. The multiple points of diversity embodied in the heterocyclic scaffold render it well-suited to the exploration of the *S′* subsites of Pr 3.[14]

An expeditious synthesis of the known sGC inhibitors ODQ and NS 2028, as well as the preparation and biological evaluation of a small library of analogues has been reported. Biological evaluation of this library using rat aortic smooth muscle cells revealed four new compounds with good to moderate sGC inhibitory activity, underlining the major importance of the oxadiazole ring in ODQ and NS 2028 for the efficiency of this class of inhibitors.[15]

An easy and convenient microwave-assisted synthesis of a small library of indolic arylpiperazine derivatives has been described. Parallel and mixed pool combinatorial methods are reported and compared, and binding assays shed additional light on the 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} receptors affinity and allowed the discovery of three interesting compounds as 5-HT_{2C}, mixed 5-HT_{2A}/5-HT_{2C} and 5-HT_{1A}/5-HT_{2C} ligands with potential antiepileptic, anxiolytic or atypical antipsychotic agent therapeutic profiles.[16]

Synthesis and evaluation of anti-TB activity of individual compounds of a Schiff base combinatorial library were done against *Mycobacterium tuberculosis* $H_{37}Rv$ at a single concentration of 6.25 μg/mL. Two compounds produced 99% inhibitory activity on the investigated organism, while the other tested compounds showed lower activity ranging from 35% to 84%.[17]

A recent study describes the identification *via* a privileged structure-based library approach of the benzhydrylpiperazine moiety as a potential scaffold to develop novel CB_1 receptor modulators. Efficient structural optimisation of the initial four hit compounds led to a high quality lead series, represented by a highly potent and selective CB_1 receptor inverse agonist that is able to reduce body weight in diet-induced obese Sprague–Dawley rats.[18]

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